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(54) Title: METHOD FOR MAKING A PROLINEBORONATE ESTER		
(57) Abstract A method for the preparation of esters of prolineboronic acid is described. An N-protected pyrrole (I) is lithiated at the 2-position. The lithiated species (II) is reacted with trialkylborate, to yield a protected pyrrole-2-boronic acid (III). This is reduced to form a protected prolineboronic acid (IV), which, in turn, is reacted with a diol to yield an ester (VI). With the boronic acid moiety protected by the ester group, the protecting group on the nitrogen is removed, yielding the desired prolineboronic acid ester (VII). In an alternative synthesis, a protected pyrrolidine (VIII) is lithiated at the 2-position to yield a protected 2-lithio-pyrrolidine (IX). This is reacted with trialkylborate to yield the intermediate IV. The prolineboronic acid esters so produced have a chiral center to the boron atom. Also disclosed are methods for resolving enantiomers. The final products can be coupled to activated carboxylic acids, to yield peptides having a prolineboronic acid ester, instead of an amino acid, at the C-terminus. These boronic acid peptide analogs are useful for inhibiting biologically important proteases. Several methods for removing pinanediol from pinanediol boronate esters are also disclosed.		

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METHOD FOR MAKING A PROLINEBORONATE ESTER

Field of the Invention

The invention relates to a method for making optically active prolineboronate esters. These are useful as intermediates in the production of peptides which incorporate prolineboronic acid instead of proline. These peptides, in turn, are useful for inhibiting various biologically important proteases.

Background of the Invention

Interest in boronic acid analogs of α -amino acids, as well as peptides incorporating a boronic acid analog of an α -amino acid instead of the C-terminal residue, has been generated by reports that these compounds are efficient inhibitors of many serine proteases. See, for example, Matteson et al. [J. Am. Chem. Soc. 103, 5241 (1981)]; Kettner et al. [J. Biol. Chem. 259, 15106 (1984)]; and, Kinder et al. [J. Med. Chem. 27, 1919 (1985)].

Several workers, including Koehler et al. [Biochemistry, 10, 2477 (1971)] and Rawn et al. [Biochemistry, 13, 3124 (1974)] have hypothesized that the empty p-orbital centered at boron in these compounds interacts with an active-site hydroxyl group of the enzyme, to form a tetrahedral adduct that mimics the transition state of enzymatic hydrolysis. It is thought that the boronic acid analog binds more tightly to the enzyme than does the substrate itself, thereby inhibiting enzymatic action upon the substrate.

The boronic acid analogs of α -amino acids and peptides incorporating them are currently of use in research because they are able to shed light on the biological functions of the enzymes they inhibit. Further, as explained below, they are also therapeutically useful.

Peptides which incorporate the α -aminoboronic acid analog of proline (BoroPro) at the C-terminus are of special interest because they have been shown to be potent inhibitors of certain post-proline cleaving enzymes. For example, Bachovchin et al. [J. Biol. Chem. 265, 3738 (1990)] have reported that such peptides are inhibitors of IgA proteinases from certain bacteria. These enzymes are strongly implicated in bacterial virulence. Flentke et al. [Proc. Natl. Acad. Sci. USA 88, 1556 (1991)] have reported that such peptides inhibit dipeptidyl peptidase IV (DP-IV), which in turn causes inhibition of antigen-induced proliferation and IL-2 production in T-cells. The latter effects are known to result in suppression of the immune response. Suppression of the immune response is, in turn, useful in the treatment of, for example, organ transplant rejection, graft versus host disease, and various autoimmune diseases.

Previous synthetic routes to α -amino boronic acids rely on the procedure published in 1981 by Matteson et al., supra, which follows the sequence of hydroboration, (asymmetric) homologation with chloromethyl lithium, and aminolysis. Matteson et al. [Organometallics 3, 1284 (1984)] have described the use of this technique to synthesize the boronic acid

analogues of N-acetylalanine, N-acetylvaline, N-acetylleucine, and N-acetylphenylalanine; some of these have been obtained with good (9:1) diastereomeric ratios.

The application of the Matteson procedure to the synthesis of BoroPro has been demonstrated by Bachovachin, supra, and Flentke, supra, but the extensive modifications required for the construction of the pyrrolidine ring render it unappealing. Furthermore, conditions for the preparation of a single enantiomer of BoroPro, either by asymmetric synthesis or by resolution, have not been reported.

Efforts to explore further the biochemistry of the post-proline cleaving enzymes, particularly DP-IV, and the possible therapeutic uses of BoroPro-based enzyme inhibitors, have been hampered by the lack of an efficient route to prolineboronic acid.

The need for a better source of BoroPro led us to explore alternate routes to this compound, especially the compound in its optically active form, and has resulted in the present invention.

Summary of the Invention

A first broad aspect of the present invention comprises three closely related methods for the synthesis of prolineboronic acid esters. Two of these syntheses commence from pyrrole. The third commences from pyrrolidine. Included within the scope of this first aspect of the invention are certain novel intermediates. Prolineboronic acid has a chiral

center α to the boron atom. A second broad aspect of the invention comprises a method for resolving the enantiomers of prolineboronic acid, if desired. According to this method, the prolineboronic ester is formed through reaction with a chiral alcohol, with the use of pinanediol being particularly preferred. Resolution of enantiomers is facilitated by separating the diastereomeric mixture resulting from the introduction of additional chiral centers. The resulting prolineboronic acid esters can be easily coupled to activated carboxylic acid groups, such as are typically used in peptide synthesis, to yield peptides having a prolineboronic acid ester, instead of an amino acid, at the C-terminus. The ester protecting group can be removed to yield the free boronic acid peptide. When the ester protecting group is pinanediol, it is not easily removed by known *per se* techniques. A third aspect of the invention comprises several methods for removing the pinanediol protecting group.

Brief Description of the Drawing

Figure 1 illustrates a reaction scheme which is a preferred embodiment of the invention.

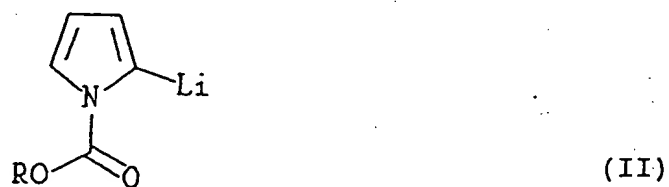
Detailed Description of the Invention

A first synthesis according to the invention commences with pyrrole, which is reacted with an activated derivative of carbonic acid, in order to protect the nitrogen atom with a group of the formula $-\text{COOR}$, wherein R is C_{1-6} alkyl, C_{3-6} cycloalkyl, benzyl, phenyl, phenyl substituted with one or more C_{1-6} alkyl groups, or trimethylsilylethyl, in order to yield a compound of the formula I.



In the preferred protecting groups, R is tert-butyl, benzyl, trimethylsilylethyl, phenyl, methyl or ethyl. The most preferred protecting group is tert-butyloxycarbonyl, or Boc. The protecting group is applied using well known techniques. A specific synthesis for 1-Boc-pyrrole has been described by Grehn et al. [Angew. Chem. Int. Ed. Engl. 23, 296 (1984)].

The compound of formula I is next treated with a lithiating agent to yield a compound of the formula II

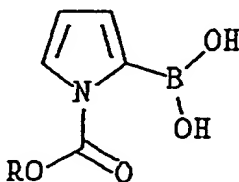


wherein R is defined as before.

Lithiation of the compound of formula I can be accomplished by treatment with lithium tetramethylpiperidide in a known per se manner, such as that described by Hasan et al. [J. Org. Chem. 46, 157 (1981)], or with other hindered lithium amides such as lithium diisopropyl amide or lithium dicyclohexylamide, or with n-butyl lithium in the

presence of tetramethyl ethylenediamine. This reaction is conveniently carried out in an inert solvent, preferably an ether such as THF, diethyl ether, dimethoxyethane, or methyl t-butyl ether at a temperature between -78°C and -40°C . Alternatively, pyrrole can be brominated at the 2-position, in a known per se manner, such as that described by Chen et al., [Org. Syn., 70, 151 (1991)], and the resulting product can be protected and then lithiated, using other less expensive lithiating agents, such as n-butyl lithium, using known per se techniques.

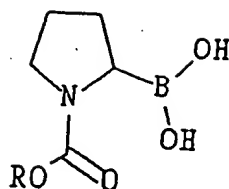
The intermediate of formula II, which is not isolated, is next reacted with a trialkyl borate wherein each alkyl group may be straight, branched or cyclic and contains 1 to 6 carbon atoms, preferably trimethyl or triethyl borate, followed by acid-catalyzed hydrolysis, using a weak acid such as citric or acetic acid, or potassium hydrogen sulfate, in order to yield a protected pyrrole-2-boronic acid of formula III



(III)

wherein R is defined as before.

The intermediate of formula III is next reduced, using catalytic hydrogenation, to form a protected prolineboronic acid of the formula IV

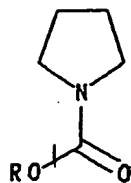


(IV)

wherein R is defined as before.

The catalytic hydrogenation of the intermediate of formula III may be carried out in an organic solvent, such as ethyl acetate or tetrahydrofuran, using a catalyst such as 5% platinum on carbon, platinum oxide, rhodium on carbon, rhodium on alumina, palladium on carbon, or Raney nickel, either at atmospheric pressure, or at about 50 psi.

An alternative synthesis of the boronic acid of formula IV uses pyrrolidine which is treated with a suitable acylating agent, to yield a protected compound of the formula VIII

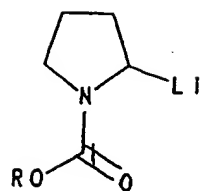


(VIII)

wherein R is defined as before.

The protecting group is chosen to allow activation of the pyrrolidine to lithiation adjacent to the nitrogen, and it should contain a bulky moiety which hinders attack on the carbonyl by the lithiating agent. It is preferred to use a carbamoyl protecting group of the formula -COOR, for example, groups wherein R is tert-butoxy or 2,4,6-tri-tert-butylphenoxy. However, certain acyl or aroyl groups can also be used, for example tert-butylcarbonyl or triphenylmethylcarbonyl. Other suitable activating groups are outlined in Beak et al., [Chem. Rev., 84, 471-523, (1984)]. The most preferred protecting group is tert-butyloxycarbonyl, or Boc. The protecting group may be applied to pyrrolidine by well known techniques.

The compound of formula VIII is next treated with a lithiating agent to yield a compound of the formula IX.



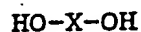
(IX)

wherein R is defined as before.

Lithiation of the compound of formula VIII can be accomplished by treatment with sec-butyl lithium and tetramethyl ethylenediamine in a known per se manner, such as that described by Beak et al. [Tet. Lett. 30, 1197 (1989)]. This reaction is conveniently carried out in an inert organic solvent, preferably an ether such as diethyl ether, methyl tert-butyl ether or THF at a temperature between about -78°C and 0°C, preferably -78°C to -40°C. Lithiation may be achieved with a reactive alkyl lithium such as sec-butyl lithium or tert-butyl lithium, preferably in the presence of a coordinating additive such as tetramethyl ethylenediamine, hexamethyl phosphoramide or N,N'-dimethylpropyleneurea (DMPU).

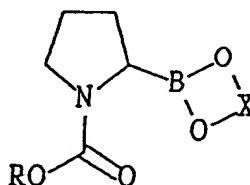
The intermediate of formula IX, which is not isolated, is next reacted with a trialkyl borate wherein each alkyl group may be straight, branched or cyclic and contains 1 to 6 carbon atoms, preferably trimethyl or triethyl borate, followed by hydrolysis with water and extraction into aqueous alkali such as sodium hydroxide or potassium hydroxide to aid purification. Acidification of the alkali solution to about pH 3 and extraction yields the protected prolineboronic acid of formula IV.

In order to form a boronic acid ester, the free boronic acid intermediate of formula IV, is next esterified by reaction with a diol of the formula V,



(V)

wherein X is a linking group, to yield a compound of the formula VI



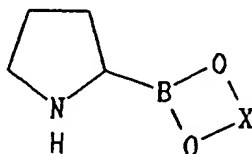
(VI)

wherein X is the same linking group mentioned above and R is defined as before. The ester group thus formed is intended to function only as a removable protecting group. The structures, syntheses, and methods for attachment and removal of such ester protecting groups are generally known in the chemical art. Accordingly, those skilled in the chemical art will appreciate that the structure of the linking group X is not critical. The linking group X can be, by way of non-limiting examples, a saturated 2- to 3-membered hydrocarbon chain; a saturated 2- to 3-membered hydrocarbon chain which constitutes part of a C₅₋₁₂ carbocyclic system which may optionally contain unsaturations or ring fusions; a 2- to 3-membered hydrocarbon chain which constitutes part of an aromatic ring system; or, a group of the formula

$-(CH_2)_n-NH-(CH_2)_m-$, wherein n and m are each 2 or 3; wherein such groups may be unsubstituted or substituted by one or more C_{1-3} alkyl or phenyl groups.

Accordingly, suitable diols of formula V are, for example, ethylene glycol, pinacol, catechol, pinanediol, butan-2,3-diol, 2,2-dimethyl propan-1,3-diol, diethanolamine and 1,2-diphenylethan-1,2-diol.

With the boronic acid moiety protected by the ester group, the protecting group on the nitrogen is next removed using known per se techniques, such as those described by Greene in "Protective Groups in Organic Synthesis" (J. Wiley & Sons, 1981), to yield the hydrochloride of the desired prolineboronic acid ester of the formula VII.



(VII)

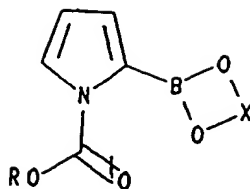
For example, when the protecting group is Boc, it may be easily removed with dry hydrogen chloride in ethyl acetate.

It is preferred to perform the esterification of the compound of formula IV with a chiral, non-racemic diol such as (1S,2S,3R,5S)-(+)-pinanediol, 1,2-diphenylethan-1,2-diol or butan-2,3-diol, because so doing introduces additional chiral centers into the molecule. This permits resolution of the chiral

center α to the boron atom, using known per se methods for separation of diastereomers, such as HPLC, or fractional crystallization. This is illustrated in the reaction scheme of Figure 1, where the isomers of the compound of formula VI in which the boronic acid is protected with (1S,2S,3R,5S)-(+)-pinanediol can be separated by HPLC to give compounds VIa and VIb. Alternatively, the isomers of the hydrochloride of the compound of formula VII, with the same boron protecting group, may be separated by fractional crystallization in a solvent such as ethyl acetate, or a dichloromethane/ethyl acetate mixture, isopropanol, or ethanol to give compound VIIb as a single isomer with the R configuration at the carbon attached to boron.

A further advantage of using pinanediol is that the boronate esters so formed are more stable than those derived from other diols, for example, pinacol, with which significant loss of the protecting group is often observed during chromatography. This is useful in both purification and isomer separation by chromatography on silica gel, since better recovery of the desired material is achieved.

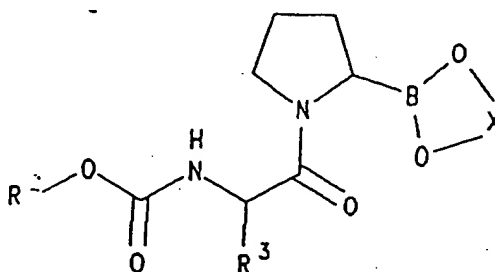
In a slight modification of the synthesis described above, a derivatized pyrrole of formula III can be directly esterified with a diol of the formula V. The resulting ester of the formula IIIA



(IIIA)

can be reduced in the same manner as the compound of formula III, yielding the protected prolineboronic acid ester of formula VI. In other words, the order of the steps in which the pyrrole ring is reduced and the boronic acid group is esterified may be reversed.

The prolineboronic acid esters thus produced are easily coupled to activated carboxylic acids such as those typically used in peptide synthesis, for example a nitrogen-protected amino acid to yield a compound of the formula X

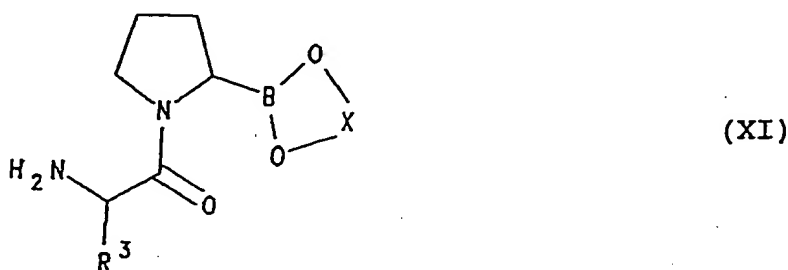


(X)

wherein -COOR^2 is an amino protecting group of the sort commonly used in peptide synthesis, so that R^2 is, for example, tert-butyl, benzyl, or fluorenylmethyl, and R^3 is the side chain of a naturally occurring amino acid, optionally with appropriate protecting groups of the sort commonly used in peptide synthesis.

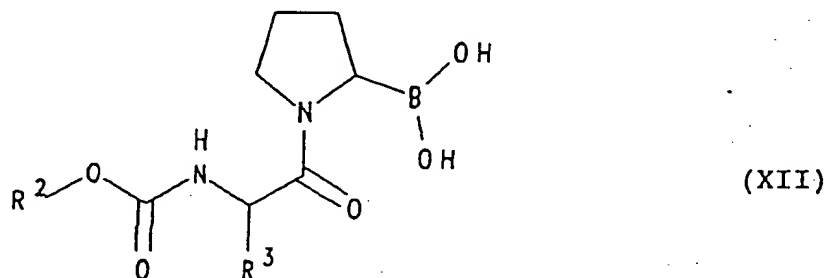
Compounds of formula X contain protecting groups both on the boronate and on the amino acid nitrogen. It may be necessary to remove either or both protecting groups for biological activity or for further chemical manipulation. The protecting groups may be removed in either order. Various methods for removing these protecting groups are described below.

Removal of the nitrogen protecting group may be achieved by known methods to yield a compound of the formula XI.



The ester group which protects the boronic acid moiety is stable to neutral and acidic organic media but many boronate esters are cleaved rapidly under mildly basic (pH = 7.5) aqueous conditions to yield the boronic acid. In the case of boronate esters of pinanediol, however, hydrolysis is known to be difficult, and special conditions are required for removal of the pinanediol. See for example Matteson et al. [J. Am. Chem. Soc., 102, 7590 (1980)] and Brown et al. [J. Organometallic Chem., 385, 15 (1988)]. These methods are not suitable for the removal of pinanediol from a compound of formula VI, X, or XI. We have found several methods for removal of pinanediol from a boronate such as compound VI, X or XI. Thus, removal

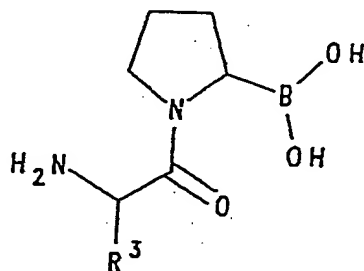
of the pinanediol may be achieved under mild conditions using an oxidizing agent capable of cleaving 1,2 diols to remove the pinanediol from the equilibrium and hence drive it in the direction of the free boronic acid. For example, treatment of compounds of formula VI and X, in which the protecting group is pinanediol, with sodium metaperiodate in aqueous ammonium acetate and acetone at ambient temperature yields compounds of formula IV and XII, respectively.



This reaction is conveniently carried out in water, optionally with an added buffer such as ammonium acetate or disodium hydrogen phosphate, at a pH between 3 and 10, preferably 6 to 8, and a temperature of 0 to 80 °C, preferably 20 to 40 °C, in the presence of a water miscible organic cosolvent such as acetone, methanol, ethanol, THF, or acetonitrile. Suitably the oxidizing agent is a non-nucleophilic oxidant capable of cleaving 1,2-diols such as periodic acid or its salts or permanganate salts. Under these conditions oxidative cleavage of the carbon-boron bond is not observed. It will be appreciated that this method is applicable to any boronic acid protected with pinanediol. Furthermore, it is applicable to any boronate protecting group which is a 1,2-diol,

although it is particularly useful for protecting groups where simple aqueous hydrolysis is slow or incomplete.

In the case of a pinanediol boronate ester of a compound containing an unprotected amine, such as a compound of formula XI, the method described above may also be employed, but a second new method is preferable for compounds of this type. This method consists of applying an aqueous solution of a compound of formula XI, at pH 4 or lower, to a column of a cation exchange resin, and eluting the column with water or dilute acetic acid to remove the pinanediol. This removes the pinanediol from the equilibrium, and thus drives the reaction in the direction of hydrolysis. The column is then eluted with dilute aqueous ammonium hydroxide to remove the product, which after evaporation and acidification is obtained as a salt of the compound of formula XIII.



(XIII)

Suitably, a strongly acidic cation exchange resin, for example a sulfonic acid type of resin is used, such as, for example, Dowex 50. The pinanediol eluted from the resin may be recovered from the water solution and reused. This is most conveniently achieved by passing the water solution through a

column of a nonionic polymeric adsorbent, such as Amberlite[®] XAD-200, which adsorbs pinanediol almost quantitatively. The pinanediol is removed from the column by elution with methanol or ethanol. The two operations of ion exchange and pinanediol adsorption may be combined in a single process in which water is recycled from one column to the other using a pump. This has the advantage of requiring much smaller amounts of water, and allows the process to be continued long enough to achieve a high conversion to the product.

Persons skilled in the art will appreciate that the above-described method for removing pinanediol using a cation exchange resin is only appropriate for compounds containing a basic functional group, such as an unprotected amine.

A third method is also applicable to pinanediol esters of compounds containing an unprotected amine, such as a compound of the formula XI. This method consists of transesterification of the pinanediol boronate with another boronic acid of the formula $R^4-B(OH)_2$, in a two-phase system. R^4 represents a C_{1-12} hydrocarbon group, which may be composed of straight, branched or cyclic alkyl chains and phenyl rings. R^4 is preferably phenyl. One of the phases is water adjusted to a pH below 7, preferably pH 1-4, and the other is a hydrocarbon organic solvent such as hexane, petroleum ether, or toluene. Thus, treatment of a compound of formula XI with phenylboronic acid in a mixture of water at pH 1 and hexane, followed by separation of the phases, produces the pinanediol ester of phenylboronic acid in the organic phase,

which may be recovered simply by evaporation, and a solution of the free boronic acid of formula XIII in the aqueous phase, which may be isolated using an ion exchange resin in a similar manner to that described above. In this system the only component which is soluble in the organic phase is the pinanediol phenylboronate, thus removing the pinanediol from the equilibrium. The compound of formula XI, and the compound of formula XIII which is formed, both remain in the aqueous layer, since neither are soluble in hydrocarbon solvents. The reaction may be carried out with any boronic acid with a hydrocarbon sidechain, providing its pinanediol ester is soluble in hydrocarbon solvents.

The fully deprotected compound of formula XIII may also be prepared by removal of the nitrogen protecting group from a compound of the formula XII using known methods. It will be appreciated that compounds of formula X, XI, XII, and XIII generally possess two chiral centers. One is adjacent to the boron atom, and the other is present in the amino acid moiety, except when that moiety is glycine. It will be further appreciated that the pure single diastereoisomers of these compounds are more desirable for biological use than mixtures of diastereoisomers. Accordingly it is important to be able to produce these compounds as pure single isomers. In principal, since amino acids are generally available as single enantiomers, this may be achieved by separating the mixture of diastereoisomers formed by coupling an optically pure amino acid with racemic prolineboronic acid, using known techniques. Nevertheless, it has

been found that, except in the special case of valine, such separations are often difficult and time consuming. Thus it is preferable to use a form of prolineboronic acid which is a single isomer at the chiral center adjacent to boron, since no isomer separation is then necessary after coupling to an optically pure amino acid. The present invention provides an easy means for resolving the enantiomers of prolineboronic acid.

The following examples further illustrate the invention.

Example 1

1-(1,1-Dimethylethoxycarbonyl)-pyrrole-2-boronic acid

To a solution of tetramethylpiperidine (8.8 mL, 52 mmol) in THF (275 mL) at -78°C under an argon atmosphere was added a 2M solution of butyllithium in hexanes (26 mL, 52 mmol). After 15 min, 1-(1,1-dimethylethoxycarbonyl)-pyrrole (8.35 g, 50mmol) in THF (10 mL) was added and the solution was stirred for 4 h at -78°C . Triethylborate (30 mL, 176 mmol) was then added and the mixture was allowed to warm to room temperature over 3 h. After an additional 12 h the reaction mixture was diluted with ether (500 mL) and washed with 1M aqueous KHSO_4 (3 x 100 mL) followed by 1M aqueous NaHCO_3 (1 x 100 mL). Drying over MgSO_4 and rotary evaporation produced a brown solid which was purified by flash chromatography over silica gel (1:9 EtOAc:Hexane) to yield 8.7 g (82%) of a white crystalline solid (mp 101.0°C - 101.5°C).

^1H NMR (CDCl_3) δ 1.65 (s, 9 H), 6.26 (t, $J = 3.3$ Hz, 1 H), 7.10 (dd, $J = 1.6, 3.2$ Hz, 1H), 7.15 (s, 2 H), 7.44 (dd, $J = 1.6, 3.2$ Hz, 1H); ^{13}C NMR (CDCl_3) 27.9, 85.5, 112.0, 127.0, 128.7, 152.0; CIMS m/z (% rel int) 212 (MH $^+$, 11), 156 (100), 138 (68); Anal. Calcd for $\text{C}_9\text{H}_{14}\text{BNO}_4$: C, 51.23, H, 6.69, N, 6.64. Found: C, 51.22, H, 6.51, N, 6.67.

Example 2

1-(1,1-Dimethylethoxycarbonyl)-pyrrolidine-2-boronic acid

A solution of 6.15 g (24 mmol) of 1-(1,1-dimethylethoxycarbonyl)-pyrrole-2-boronic acid, produced as in Example 1, in EtOAc (100 mL) was hydrogenated over 5% Pt / C (ca. 500 mg) at 50 psi for 24 to 48h. The resulting suspension was filtered through a pad of Celite and concentrated. This material was chromatographed on silica gel using sequential elutions of 9:1 hexanes:EtOAc then acetone. The acetone fractions were concentrated to produce 6.05 g (97%) of the desired compound as a clear glass that crystallized upon removal of trace solvents (mp 100-101 $^{\circ}\text{C}$).

^1H NMR (CDCl_3): δ 1.42 (s, 9 H), 1.6 - 2.15 (m, 5 H), 3.1 - 3.6 (m, 2 H); ^{13}C NMR (CDCl_3) δ 25.1, 25.7, 28.4, 45.6, 46.2, 78.6, 154.5; CIMS m/z (% rel int) 116 (100), 70 (46); Anal. Calcd for $\text{C}_9\text{H}_{18}\text{BNO}_4$: C, 50.27, H, 8.44, N, 6.51. Found: C, 50.52, H, 8.22, N, 6.58.

Example 3

(1S,2S,3R,5S)-Pinanediol 1-(1,1-dimethylethoxy-carbonyl)-pyrrolidine-2S-boronate and
(1S,2S,3R,5S)-Pinanediol 1-(1,1-dimethyl-ethoxycarbonyl)-pyrrolidine-2R-boronate

A solution of 1-(1,1-dimethylethoxycarbonyl)-pyrrolidine-2-boronic acid, produced as in Example 2, (1.52 g, 7.1 mmol) and (1S,2S,3R,5S)-(+)-pinanediol (1.36 g, 8.0 mmol) was stirred at room temperature in ether (25 mL) for 2 h. Concentration and flash chromatography over silica gel (85:15 hexanes:EtOAc) produced 2.1 g (85%) of a 1:1 mixture of the two diastereomers. These were separated by HPLC over a 300 X 3.9 mm column of microporasil A eluting with methyl tert-butyl ether:hexanes (1:9) and using u.v. detection at 220 nm. The isomer (1S,2S,3R,5S)-pinanediol 1-(1,1-dimethyl-ethoxycarbonyl)-pyrrolidine-2S-boronate eluted first under these conditions.

S-isomer: ^1H NMR (C_6D_6): δ 0.55 (s, 3 H), 1.09 (s, 3 H), 1.52 (s, 9 H), 1.60 (s, 3 H), 1.2 - 2.2 (m, 8 H), 3.1 - 3.5 (m, 3 H), 4.11 (m, 0.3 H), 4.33 (m, 0.7 H); ^{13}C NMR (C_6D_6): δ 23.9, 26.6, 27.1, 27.3, 28.4, 28.6, 28.8, 36.0, 38.2, 39.9, 46.1, 51.9, 78.3, 78.5, 85.7, 154.9.

R-isomer: ^1H NMR (C_6D_6): δ 0.52 (s, 3 H), 1.08 (s, 3 H), 1.52 (s, 9 H), 1.61 (s, 3 H), 1.2 - 2.2 (m, 8 H), 3.1 - 3.6 (m, 3 H), 4.01 (m, 0.3 H), 4.25 (m, 0.7 H); ^{13}C NMR (C_6D_6) 23.9, 26.6, 27.1, 27.3, 28.4, 28.7, 28.9, 35.8, 38.2, 39.6, 46.2, 51.8, 78.1, 78.5, 85.7, 154.5.

It will be recognized that (1R,2R,3S,5R)-pinanediol-1-(1,1-dimethylethoxycarbonyl)-pyrrolidine-2S-boronate and (1R,2R,3S,5R)-pinanediol-1-(1,1-dimethylethoxycarbonyl)-pyrrolidine-2R-boronate could be produced in an analogous manner, starting with (1R,2R,3S,5R)-(-)-pinanediol.

Example 4

(1S,2S,3R,5S)-Pinanediol pyrrolidine-2S-boronate hydrochloride

A solution of (1S,2S,3R,5S)-pinanediol-1-(1,1-dimethylethoxycarbonyl)-pyrrolidine-2S-boronate, produced as in Example 3 (28.5 mg, 0.08 mmol) was stirred in a solution of dry HCl in EtOAc (approximately 3M). After 2 h the solution was concentrated twice from EtOAc to produce 21.2 mg (91%) of the desired hydrochloride as a white solid (mp 204°C (dec)).

^1H NMR (CDCl_3): δ 0.83 (s, 3 H), 1.14 (d, J = 11Hz, 1 H), 1.29 (s, 3 H), 1.45 (s, 3 H), 1.85 - 2.15 (m, 6 H), 2.17 - 2.50 (m, 3 H), 3.18-3.25 (m, 1 H), 3.45 (bs, 2 H), 4.42 (dd, J = 1.8, 8.6Hz, 1 H), 8.80

(bs, 1H), 10.56 (bs, 1H); ^{13}C NMR (CDCl_3): δ 23.9, 24.5, 26.5, 27.0, 27.2, 28.4, 34.9, 38.2, 39.4, 45.8, 51.2, 79.0, 87.6; CIMS m/z (% rel int) 250 (MH^+ , 100); HRMS (EI) for $\text{C}_{14}\text{H}_{24}\text{BNO}_2$ calcd 249.1900, found 249.1899.

It will be recognized that (1R,2R,3S,5R)-pinanediol-pyrrolidine-2S-boronate hydrochloride could be made in an analogous manner.

Example 5

(1S,2S,3R,5S)-Pinanediol pyrrolidine-2R-boronate hydrochloride

A solution of (1S,2S,3R,5S)-pinanediol-1-(1,1-dimethylethoxycarbonyl)-pyrrolidine-2R-boronate, produced as in Example 3 (18.3 mg, 0.05 mmol) was treated with dry HCl in EtOAc as above. Work-up produced 14.3 mg (96%) of the desired hydrochloride as a white solid (mp 248 °C (dec)).

^1H NMR (CDCl_3): δ 0.83 (s, 3 H), 1.14 (d, J = 11Hz, 1 H), 1.29 (s, 3 H), 1.45 (s, 3 H), 1.85 - 2.15 (m, 6 H), 2.17 - 2.50 (m, 3 H), 3.18-3.25 (m, 1 H), 3.45 (bs, 2 H), 4.42 (dd, J = 1.8, 8.6Hz, 1 H), 8.80 (bs, 1 H), 10.56 (bs, 1 H); ^{13}C NMR (CDCl_3) δ 23.9, 24.5, 26.5, 27.0, 27.2, 28.5, 34.9, 38.1, 39.4, 45.8, 51.2, 79.0, 87.8; CIMS m/z (% rel int) 250 (MH^+ , 100); HRMS (EI) for $\text{C}_{14}\text{H}_{24}\text{BNO}_2$ calcd 249.1900, found 249.1903.

It will be recognized that (1R,2R,3S,5R)-pinanediol pyrrolidine-2R-boronate hydrochloride could be made in an analogous manner.

Example 6

(1S,2S,3R,5S)-Pinanediol

1-(1,1-dimethylethoxycarbonyl)-pyrrole-2-boronate

A solution of 1-(1,1-dimethylethoxycarbonyl)-pyrrole-2-boronic acid, produced as in Example 1 (1.36 g, 6.45 mmol) and (1S,2S,3R,5S)-(+)-pinanediol (1.10 g, 6.45 mmol) was stirred in 20 mL of ether for 4 h. Rotary evaporation followed by flash chromatography over silica gel (95:5 hexane:EtOAc) produced 1.83 g (82%) of the desired product as a clear oil.

^1H NMR (CDCl_3): δ 0.90 (s, 3 H), 1.30 (s, 3 H), 1.41 (d, $J = 11$ Hz, 1 H), 1.50 (s, 3 H), 1.50 (s, 3 H), 1.59 (s, 9 H), 1.96 (m, 2 H), 2.21 (t, $J = 6$ Hz, 1 H), 2.16 - 2.40 (m, 2 H), 4.45 (dd, $J = 2, 8$ Hz, 1 H), 6.20 (t, $J = 3$ Hz, 1 H), 6.65 (d, $J = 3$ Hz, 1 H), 7.40 (d, $J = 3$ Hz, 1 H); ^{13}C NMR (CDCl_3): δ 24.0, 26.4, 27.2, 28.1, 28.6, 35.5, 38.3, 39.8, 51.8, 79.8, 83.6, 83.9, 111.6, 123.2, 124.7, 150.0; CIMS m/z (% rel int) 346 (MH^+ , 4), 246 (81), 153 (100), 135 (56).

It will be recognized that (1R,2R,3S,5R)-pinanediol-1-(1,1-dimethylethoxycarbonyl)-pyrrole-2-boronate could be made in an analogous manner.

Example 71-(1,1-Dimethylethoxycarbonyl)-pyrrolidine-2-boronic acid from 1-(1,1-dimethylethoxycarbonyl)-pyrrolidine

To a solution of 1-(1,1-dimethylethoxycarbonyl)-pyrrolidine (17.1 g, 100 mmol) in diethyl ether (200 mL) at -78 °C under an atmosphere of nitrogen was added 1.3M sec-butyllithium in cyclohexane (92.3 mL, 120 mmol) whilst maintaining the temperature below -60 °C. After addition was complete, the reaction mixture was stirred at -78 °C for 4 h.

Trimethylborate (31.1 g, 300 mmol) was added and the mixture was allowed to warm to room temperature over 3h. After an additional 12h, water (150 mL) was added followed by 2M NaOH (200 mL). The aqueous phase was isolated and the organic phase was reextracted with 2M NaOH (150 mL). The combined basic extracts were acidified to pH 3 using 2M HCl and extracted using EtOAc (5 x 200 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to afford the desired product as a white crystalline solid (15.49g, 72%), identical with the material produced in Example 2.

Example 8(1S,2S,3R,5S)-Pinanediol1-(1,1-dimethylethoxycarbonyl)-pyrrolidine-2RS-boronate

To a stirred solution of the material obtained in Example 7 (15.49 g, 72.0 mmol) in chloroform (250 mL) was added (1S,2S,3R,5S)-(+)-pinanediol (12.77 g,

75 mmol). After stirring at room temperature under a nitrogen atmosphere for 16 h, the solvent was removed and the residue purified via flash chromatography over silica gel (hexane/EtOAc 9:1, 4:1) to give the desired product as a 1:1 mixture of diastereomers as an oil (23.62 g, 67.7% based on 1-(1,1-dimethylethoxycarbonyl)-pyrrolidine). This was identical with the mixture of isomers produced in Example 3.

^1H NMR (CDCl_3): δ 0.85 (s, 3H), 1.12-1.21 (m, 1H), 1.29 (s, 3H), 1.41 (s, 3H), 1.45 (s, 9H), 1.81-2.20 (m, 8H), 2.28-2.39 (m, 1H), 3.04-3.18 (m, 1H), 3.34-3.45 (m, 2H), 4.28-4.38 (m, 1H); ^{13}C NMR (CDCl_3): δ 23.7, 26.2, 27.1, 28.5, 35.5, 38.2, 39.6, 46.1, 78.0, 78.8, 85.7, 85.8, 154.7; CIMS m/z (% rel int) 350 (MH $^+$, 100), 294 (72), 250 (30).

Example 9

Analytical Method for the Diastereoisomers of (1S,2S,3R,5S)-Pinanediol pyrrolidine-2-boronate hydrochloride.

A reagent solution of 0.2 M phenyl isothiocyanate in dichloromethane-triethylamine (9:1) was prepared. The sample to be analyzed (1-5 mg) was treated with 10 μL of the reagent solution per μmole of analyte and the clear solution was allowed to stand at room temperature for 15 min. A 1 μL sample of the solution was then diluted in 1.00 mL of HPLC-grade acetonitrile and 10 μL of this solution was analyzed by HPLC (column: YMC AQ-303 S-5 120A, 4.6 x 250 mm;

mobile phase: 65% MeCN - 35% 25 mM ammonium phosphate, pH 7.5; flow rate 1 mL/min; detection by UV at 254 nm). The phenylthiourea derivative of the R isomer of proline boronic acid elutes at about 6.4 min, its epimer elutes at about 7.8 min, and unreacted phenyl isothiocyanate, which serves as an internal standard, elutes at 12.2 min.

Example 10

(1S,2S,3R,5S)-Pinanediol pyrrolidine-2RS-boronate hydrochloride

A stirred solution of (1S,2S,3R,5S)-pinanediol 1-(1,1-dimethylethoxycarbonyl)-pyrrolidine-2RS-boronate (224 g, 0.64 mol) in diethyl ether (900 mL) was cooled in ice and dry HCl gas passed into the solution for 35 min at 10-18 °C. The solution was stirred at room temperature overnight, cooled again in ice and the precipitate filtered off. The solid was washed with cold ether (400 mL) followed by petroleum ether/diethyl ether 9:1 (200 mL) and dried under vacuum to give the desired hydrochloride as a white solid (113 g, 62%) (mp 228-234°C). Analysis of this material by HPLC as described in Example 9 showed it to be a 60:40 mixture of R:S isomers of the boronic acid.

^1H NMR (CDCl_3): δ 0.83 (s, 3 H), 1.14 (d, J = 11Hz, 1 H), 1.29 (s, 3 H), 1.45 (s, 3 H), 1.85 - 2.15 (m, 6 H), 2.17 - 2.50 (m, 3 H), 3.18-3.25 (m, 1 H), 3.45 (bs, 2 H), 4.42 (dd, J = 1.8, 8.6Hz, 1 H), 8.80 (bs, 1 H), 10.56 (bs, 1 H); ^{13}C NMR (CDCl_3) δ 23.9, 24.5, 26.5, 27.0, 27.2, 28.4, 34.9, 38.2, 39.4, 45.8, 51.2, 79.0, 87.6; CIMS m/z (% rel int) 250 (MH⁺, 100); Anal. Calcd for $\text{C}_{14}\text{H}_{24}\text{BNO}_2 \cdot \text{HCl}$: C, 58.87, H, 8.82, N, 4.90, Cl, 12.41. Found: C, 58.40, H, 8.86, N, 4.81, Cl, 12.39.

A similar reaction on a 29 g, 101 mmol scale using ethereal HCl (approx. 4.5M, 200 mL) and EtOAc (150 mL) as solvent yielded the hydrochloride (11.1 g, 47%) as a 81:19 mixture of R:S isomers

Example 11

(1S,2S,3R,5S)-Pinanediol pyrrolidine-2R-boronate hydrochloride by fractional crystallization.

Method A:

The 60:40 isomeric mixture obtained in Example 10 (1.18 g 4.13 mmol) was dissolved in CH_2Cl_2 (65 mL) with slight warming, and the solution filtered. The filtrate was diluted with EtOAc (65 mL) and crystallization began within a minute. The suspension was stirred for 1-2 h at room temperature and the first crop of solid was collected and the diastereomeric ratio determined as described in Example 9 (540 mg, 46%, R:S ratio 97.1:2.9). Solvent

was distilled from the filtrate until most of the CH_2Cl_2 was removed, then the residual EtOAc solution was stirred at room temperature overnight to afford a second crop of off-white solid (346 mg, 29%, R:S ratio 39.2:60.8). The first crop was recrystallized from isopropyl alcohol (10 mL) to afford 430 mg (80% recovery) of material >99% 2-R isomer. (mp 269-272 °C (dec)) $[\alpha]_{25}^D +0.70^\circ$ (c=1.15, MeOH)

^1H NMR (CDCl_3): δ 0.83 (s, 3 H), 1.14 (d, J = 11Hz, 1 H), 1.29 (s, 3 H), 1.45 (s, 3 H), 1.85 - 2.15 (m, 6 H), 2.17 - 2.50 (m, 3 H), 3.18-3.25 (m, 1 H), 3.45 (bs, 2 H), 4.42 (dd, J = 1.8, 8.6Hz, 1 H), 8.80 (bs, 1 H), 10.56 (bs, 1 H); ^{13}C NMR (CDCl_3) δ 23.9, 24.5, 26.5, 27.0, 27.2, 28.5, 34.9, 38.1, 39.4, 45.8, 51.2, 79.0, 87.8; CIMS m/z (% rel int) 250 (MH⁺, 100); Anal. Calcd for $\text{C}_{14}\text{H}_{24}\text{BNO}_2 \cdot \text{HCl}$: C, 58.87, H, 8.82, N, 4.90, Cl, 12.41. Found: C, 58.64, H, 8.79, N, 4.90, Cl, 12.66.

Method B:

A suspension of (1S,2S,3R,5S)-pinanediol-pyrrolidine-2RS-boronate hydrochloride as a 1:1 mixture of isomers (850 mg, 2.98 mmol) in EtOAc (60 mL) was heated under reflux with stirring for 4 h. The mixture was filtered hot and the collected solid dried to give material enriched in the R isomer (541 mg 64%), R:S ratio 2:1. Evaporation of the filtrate yielded material enriched in the S isomer (217 mg), R:S = 1:4. The filtered solid (500 mg) was treated in the same way with EtOAc (45 mL) for 1.5 h and again filtered hot to yield a solid (366 mg, 73%), R:S = 7:1. This material was again treated with EtOAc

(38 mL) for 1.5 h. The solid isolated (287 mg, 78%) now had R:S ratio 97:3. The spectral properties were the same as those of material obtained by method A.

Example 12

1-(1,1-Dimethylethoxycarbonyl)-pyrrolidine-2-boronic acid from (1S,2S,3R,5S) pinanediol
1-(1,1-dimethylethoxycarbonyl)-pyrrolidine-2-boronate

To a solution of (1S,2S,3R,5S)-pinanediol-1-(1,1-dimethylethoxycarbonyl)-pyrrolidine-2RS-boronate from Example 8 (1.9 g, 5.44 mmol) in acetone (80 mL) was added 0.1M ammonium acetate solution (80 mL) and sodium metaperiodate (3.49 g, 16.33 mmol). The reaction mixture was stirred at room temperature for 40 h, then the acetone was evaporated and the residue was treated with 2M NaOH solution. This aqueous phase was washed with CH_2Cl_2 (2 x 80 mL), acidified with 2M HCl to pH 3 and extracted with CH_2Cl_2 (4 x 80 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to afford the desired product as a white foamy solid (890 mg, 76%), identical by NMR with the material prepared in Example 2. The boronic acid was derivatized with pinacol for purposes of analysis.

Example 13Pinacol 1-(1,1-dimethylethoxycarbonyl)-pyrrolidine-2RS-boronate

To a stirred solution of the boronic acid from Example 12 (890 mg, 4.14 mmol) in chloroform was added pinacol (489 mg, 4.14 mmol). After stirring for 16h at room temperature, the solvent was removed and the residue was purified via chromatography over silica gel (hexane/EtOAc, 4:1) to give the desired product as a white solid (1.04 g, 85%) (mp 73-75 °C).

^1H NMR (CDCl_3): δ 1.18 (s, 6H), 1.21 (s, 6H), 1.38 (s, 9H), 1.57-2.00 (m, 4H), 2.98 (br s, 1H), 3.27 (m, 2H); ^{13}C NMR (CDCl_3): δ 24.3, 24.5, 24.7, 24.9, 25.3, 27.0, 27.6, 28.4, 28.6, 43.6, 45.8, 46.3, 78.8, 83.2, 154.4, 154.8; CIMS m/z (% rel int) 298 (18), 242 (100, $\text{MH}^+ - \text{tBu}$), 198 (30, $\text{MH}^+ - \text{Boc}$); Anal. Calcd for $\text{C}_{15}\text{H}_{28}\text{BNO}_4$: C, 60.62, H, 9.50, N, 4.71. Found: C, 60.94, H, 9.65, N, 4.88.

Example 14N-(1,1-Dimethylethoxycarbonyl)-L-valylpyrrolidine-2R-boronate (1S,2S,3R,5S)-pinanediol ester

A solution of t-BOC-L-Valine (351.7 g, 1.62 mol) in CH_2Cl_2 (1.6 L) was cooled with an ice bath and a solution of dicyclohexylcarbodiimide (161.8 g, 0.784 mol) in CH_2Cl_2 (0.75 L) was added within 40 min at 0-2 °C. After addition the solution was

stirred for 3.5 h at 0-5 °C. The white precipitate was filtered off and washed with CH_2Cl_2 (0.2 L). The resulting clear solution was added at 18-20 °C (waterbath cooling) to a solution of (1S,2S,3R,5S)-pinanediol pyrrolidine-2RS-boronate hydrochloride (210 g, 0.735 mol), prepared as in Example 10, in CH_2Cl_2 (2.0 L) containing N-methylmorpholine (164 g, 1.62 mol). The mixture was allowed to stir at room temperature overnight. The cloudy solution was filtered through a 16 cm dia. x 2 cm high bed of silica gel (200-425 mesh) and washed with CH_2Cl_2 (1.5 L). The solvent was evaporated to yield a highly viscous oil (542 g). This oil was dissolved in ethyl acetate (0.7 L) and the mixture cooled in an ice bath. Crystals formed, which were filtered off at low temperature, and washed with cold ethyl acetate (0.1 L). The wet filter cake was transferred into petroleum ether (0.65 L) and stirred at room temperature for 1 h. The white solid was filtered, washed with cold petroleum ether (0.1 L), and dried to constant weight to yield the title compound as a white solid (113.4 g) (mp 128-130 °C). All the mother liquors were combined and concentrated to a volume of approx. 0.8 L. After standing for 2 days in the freezer a solid formed, which was filtered off, and treated with petroleum ether as above to yield a beige solid (50.4 g). This was a mixture of impurities and the unwanted diastereoisomer. The mother liquor from above was concentrated and the residue purified over a silica gel column (14 cm dia. x 60cm) using hexane/ethyl acetate (85:15) (14 L). Appropriate fractions were collected, treated with petroleum ether, the solid collected by filtration and

dried, to yield more desired product (18.5 g). The other diastereoisomer was also obtained (7.5 g) (mp 82-83 °C). A second column was performed on the combined mixed fractions and mother liquors to yield additional pure compound (13.5 g), total combined yield 145.4 g (44.3%) of desired diastereoisomer (mp 128-130 °C).

^1H NMR (CDCl_3): δ 0.83 (s, 3 H), 0.91 (d, J = 6.7 Hz, 3 H), 0.97 (d, J = 6.7 Hz, 3 H), 1.27 (s, 3 H), 1.35-1.45 (m, 1 H), 1.39 (s, 3 H), 1.41 (s, 9 H), 1.72-2.14 (m, 9 H), 2.26-2.36 (m, 1 H), 3.15 (dd, J = 6.7, 10.1 Hz, 1 H), 3.43-3.51 (m, 1 H), 3.70-3.81 (m, 1 H), 4.19-4.28 (m, 2 H), 5.29 (d, J = 9.2 Hz, 1 H); ^{13}C NMR (CDCl_3): δ 17.3, 19.2, 24.0, 26.3, 27.1, 27.2, 27.4, 28.4, 28.6, 31.4, 33.9, 35.5, 38.2, 39.6, 46.7, 51.2, 56.6, 77.8, 79.2, 85.8, 155.9, 170.2; CIMS m/z (% rel int) 449 (MH $^+$, 100), 393 (50); Anal. Calcd for $\text{C}_{24}\text{H}_{41}\text{BN}_2\text{O}_5$: C, 64.28, H, 9.22, N, 6.25. Found: C, 64.58, H, 9.33, N, 6.52.

Example 15

L-valylpyrrolidine-2R-boronate

(1S,2S,3R,5S)-pinanediol ester hydrogen maleate

N-(1,1-Dimethylethoxycarbonyl)-L-valylpyrrolidine-2R-boronate (1S,2S,3R,5S)-pinanediol ester (248 mg, 0.553 mmol) was added to a stirred solution of dry hydrogen chloride in ethyl acetate. After 1.5 h the solvent was evaporated to leave the deprotected hydrochloride. The residue was partitioned between

CH_2Cl_2 and sodium carbonate solution, and the organic layer dried over magnesium sulfate. The organic layer contains the free base of the title compound, which exists as a cyclic form containing a nitrogen-boron bond, but reverts to the open form on adding acid. The organic solution was filtered into a solution of maleic acid (64 mg, 0.553 mmol) in methanol (5 mL), and the solvent evaporated to leave a crystalline residue (258 mg), which was recrystallized from ethyl acetate to give the title compound (193 mg, 75%) (mp 145-146 °C).

^1H NMR (CDCl_3): δ 0.84 (s, 3 H), 1.08 (d, J = 6.9 Hz, 3 H), 1.13 (d, J = 6.9 Hz, 3 H), 1.26-1.31 (m, 2 H), 1.29 (s, 3 H), 1.38 (s, 3 H), 1.72-2.15 (m, 7 H), 2.24-2.38 (m, 2 H), 3.28 (dd, J = 6.9, 9.4 Hz, 1 H), 3.38-3.47 (m, 1 H), 3.73-3.78 (m, 1 H), 4.14 (d, J = 5.1 Hz, 1 H), 4.26 (d, J = 7.1 Hz, 1 H), 6.25 (s, 2 H), 7.5-9.0 (v. br, 4 H); ^{13}C NMR (CDCl_3): δ 17.0, 18.4, 24.0, 26.3, 27.0, 27.1, 28.7, 30.0, 35.4, 38.2, 39.5, 47.3, 51.2, 56.6, 78.1, 86.2, 135.6, 166.3, 169.5; CIMS m/z (% rel int) 349 (MH $^+$, 100), 197 (18); Anal. Calcd for $\text{C}_{23}\text{H}_{37}\text{BN}_2\text{O}_7$: C, 59.49, H, 8.03, N, 6.03. Found: C, 59.50, H, 8.13, N, 6.03.

Example 16L-valylpyrrolidine-2R-boronic acid methanesulfonate

a) cyclo-L-valylpyrrolidine-2R-boronic acid

A solution of the maleate salt obtained in Example 15 (5.0 g, 10.8 mmol) in dilute acetic acid (1.0%, 60 mL) was loaded on to a column (3.5 cm deep x 4 cm dia.) of Dowex 50X2-200 ion exchange resin in the H⁺ form. The column was then eluted with acetic acid (1.0%, 14 L), water (42 L) and ammonium hydroxide solution (1:100 dilution of commercial 0.880 solution). Pinanediol could be recovered from the neutral and acidic fractions. The product was found in early basic fractions, which were collected and washed with CH₂Cl₂ (2 x 100 mL). The organic extracts were dried and concentrated to afford recovered free base of the starting material (741 mg, 20%), along with some pinanediol. The aqueous phase was lyophilized to afford the title compound, which exists in a cyclic form with a nitrogen-boron bond, as a white solid (1.52g, 66%) (mp 120-130°C).

¹H NMR (D₂O): δ 0.97 (d, J = 7.0 Hz, 3 H), 1.06 (d, J = 7.0 Hz, 3 H), 1.59-1.80 (m, 2 H), 1.95-2.03 (m, 2 H), 2.41-2.51 (m, 1 H), 2.62-2.69 (m, 1 H), 3.23-3.32 (m, 1 H), 3.51-3.58 (m with overlapping doublet, J = 4.2 Hz, 2 H); ¹³C NMR (D₂O): δ 19.0, 21.7, 27.3, 30.7, 29.9, 49.6, 61.0, 170.3; IR (cm⁻¹) 3400-3314, 3221-3108, 2961-2872, 1637, 1452-1369; CIMS m/z (% rel int) 375 (90,

M_2H+-3H_2O), 197 (100, $MH+-H_2O$); Anal. Calcd for $C_9H_{19}BN_2O_3$: C, 50.50, H, 8.95, N, 13.09.
Found: C, 50.43, H, 8.76, N, 12.93.

b) L-valylpyrrolidine-2R-boronic acid methanesulfonate

To a stirred suspension of the cyclized boronic acid obtained above (5.17 g, 24.16 mmol) in acetonitrile (190 mL) under nitrogen was added a solution of methanesulfonic acid (2.32 g, 24.16 mmol) in acetonitrile (10 mL) dropwise over five minutes and the mixture stirred at room temperature for 2 h. The solid was collected by filtration, washed well with acetonitrile and diethyl ether and dried to afford the title compound as a white solid (6.14g, 82%) (mp 179-180 °C). Crystallization of this material from dimethylformamide/acetonitrile gave a 70% recovery of material in a single crop (mp 181-182 °C).

1H NMR (D_2O , phosphate, pH2): δ 0.99 (d, $J = 6.8$ Hz, 3H), 1.09 (d, $J = 6.9$ Hz, 3H), 1.69-1.75 (m, 1H), 1.90-1.99 (m, 1H), 2.10-2.14 (m, 2H), 2.28-2.35 (m, 1H), 2.80 (s, 3H), 3.07 (dd, $J = 7.0$ and 11.2 Hz, 1H), 3.46-3.51 (m, 1H), 3.75 (t, $J = 9.0$ Hz, 1H), 4.14 (d, $J = 5.1$ Hz, 1H); the cis amide rotamer (ca. 3%) is also observed at 3.53-3.55 (m) and 3.83 (d, $J = 6.2$ Hz); ^{13}C NMR: δ 16.2, 18.4, 26.9, 27.1, 29.0, 38.8, 47.9, 49.0, 57.2, 167.2; peaks due to the cis amide rotamer are observed at 16.8, 24.3, 29.9, 57.8, 167.5; IR (cm^{-1}) 3387, 3000 (br), 2972, 2655, 1646, 1370, 1197; CIMS m/z (% rel int, ethylene glycol adduct) 241 ($MH+ 100$); Anal. Calcd for $C_{10}H_{23}BN_2O_6S$: C, 38.72, H, 7.47, N, 9.03.
Found: C, 38.65, H, 7.45, N, 8.44.

Example 17N-(1,1-Dimethylethoxycarbonyl)-L-valylpyrrolidine-2R-boronic acid

To a stirred solution of N-(1,1-dimethylethoxycarbonyl)-L-valylpyrrolidine-2R-boronate (1S,2S,3R,5S)-pinanediol ester, prepared as in Example 14, (1.0 g, 2.3 mmol) in acetone (75 mL) was added ammonium acetate solution (60 mL, 0.1 M) and sodium metaperiodate (1.48 g, 6.91 mmol). The reaction mixture was stirred at room temperature for 48 h, then the acetone was evaporated. The residue was treated with 2M sodium hydroxide solution (100 mL), and washed with CH_2Cl_2 (2 x 50 mL). The aqueous layer was carefully acidified with 2M hydrochloric acid to pH 3 and extracted with CH_2Cl_2 (4 x 70 mL). The combined organic extracts of the acid solution were dried over sodium sulphate and concentrated to afford the desired product as a white foamy solid (700mg, 97%). Further purification via chromatography over silica gel (CH_2Cl_2 /methanol, 9:1) gave the boronic acid again as a white solid (449 mg, 62%) (mp 82-92°C).

^1H NMR (CDCl_3): δ 0.95 (d, $J = 5.7$ Hz, 6H), 1.42 (s, 9H), 1.55-1.80 (m, 1H), 1.80-2.20 (m, 4H), 2.89-3.07 (m, 1H), 3.30-3.55 (m, 1H), 3.55-3.65 (m, 1H), 4.10-4.30 (m, 1H), 5.34 (d, $J = 9.2$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 18.0, 19.1, 26.3, 27.7, 28.3, 31.2, 46.1, 52.0, 55.7, 79.5, 155.6, 170.8; IR (cm^{-1}) 3395-3319, 2971-2875, 1711, 1619, 1400, 1174; CIMS m/z (% rel int, ethylene glycol adduct) 341(MH^+ , 100), 285(MH^+ -tBu, 67), 241(MH^+ -BOC, 21).

Example 18L-valylpyrrolidine-2R-boronic acid hydrochloride

N-(1,1-Dimethylethoxycarbonyl)-L-valylpyrrolidine-2R-boronic acid, obtained in Example 17 (250 mg, 0.796 mmol) was stirred with HCl/ether (4.5M, 20 mL) at room temperature under nitrogen for 1.5 h. The solvent was then evaporated and the residue triturated with diethyl ether (3 x 10 mL) and each time the ether was decanted. The residue was dried to yield the title compound as a white powdery solid (172 mg, 86%) (mp 211-213°C).

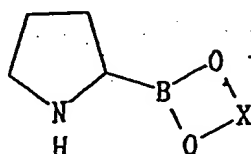
^1H NMR (D_2O , phosphate pH 2): δ 0.99 (d, J = 6.9 Hz, 3 H), 1.09 (d, J = 7.0 Hz, 3 H), 1.67-1.76 (m, 1 H), 1.87-2.01 (m, 1 H), 2.09-2.15 (m, 2 H), 2.28-2.35 (m, 1 H), 3.07 (dd, J = 7.0 and 11.4 Hz, 1 H), 3.48 (dt, J = 6.7 and 10.3 Hz, 1 H), 3.73 (dt, J = 1.7 and 10.2 Hz, 1 H), 4.14 (d, J = 5.2 Hz, 1 H); ^{13}C NMR: δ 16.0, 18.3, 26.9, 27.1, 28.9, 47.9, 48.9, 57.2, 167.3; IR (cm^{-1}) 3400-2800, 3368, 2970/2880, 1635, 1475-1378, 1400; CIMS m/z (% rel int, ethylene glycol adduct) 241 (MH^+ , 100).

Example 19cyclo-L-Valylpyrrolidine-2R-boronic acid by transesterification with phenylboronic acid

A solution of L-valylpyrrolidine-2R-boronate (1S,2S,3R,5S)-pinanediol ester hydrochloride, prepared as in Example 15 (500 mg, 1.3 mmol) in 1M hydrochloric acid (10 mL) containing hexane (20 mL) and phenylboronic acid (500 mg, 2.6 mmol) was stirred vigorously for 1h at room temperature. The hexane was removed by decantation, then more hexane (20 ml) was added and the mixture stirred for a further 30 min. The layers were separated and the combined hexane layers dried over sodium sulphate and concentrated to give pinanediol phenylboronate (331 mg, 99%) as a white crystalline solid. The aqueous layer was then passed through a column of Dowex 50 ion exchange resin. The column was eluted with water (200 mL), followed by ammonium hydroxide solution (1:100 dilution of commercial 0.880 solution, 50 ml). Isolation of the basic fractions followed by lyophilization gave the free boronic acid (230 mg, 83%) as a white powder, identical by NMR with the material obtained in Example 16a.

We Claim:

1. A method for making a prolineboronic acid ester of the formula VII

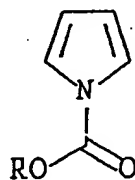


(VII)

wherein X is a linking group,

which method comprises:

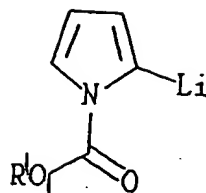
- a) treating pyrrole with an activated derivative of carbonic acid, to yield an N-protected pyrrole of the formula I



(I)

wherein R is C₁₋₆alkyl, C₃₋₆cycloalkyl, benzyl, phenyl, phenyl substituted with one or more C₁₋₆alkyl groups, or trimethylsilylethyl,

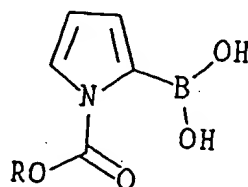
- b) treating the protected intermediate of the formula I with a lithiating agent, to yield an intermediate of the formula II



(II)

wherein R is as defined above,

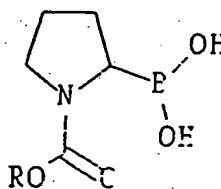
c) reacting the intermediate of formula II with a trialkyl borate, wherein each alkyl group may be straight, branched or cyclic and contains 1 to 6 carbon atoms, followed by acid catalyzed hydrolysis, to yield an intermediate of the formula III



(III)

wherein R is as defined above,

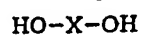
d) reducing the compound of formula III, using catalytic hydrogenation, in order to yield the proline intermediate of formula IV



(IV)

wherein R is as defined above,

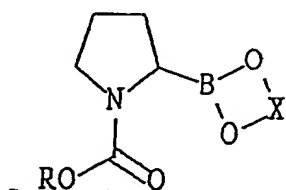
e) reacting the compound of formula IV with a diol of the formula V,



(V)

wherein X is the same linking group mentioned above,

to yield a boronate ester of the formula VI



(VI)

wherein X is the same linking group mentioned above and R is as defined above, and

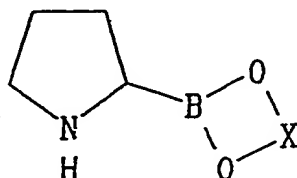
f) removing the protecting group from the nitrogen atom in the proline ring.

2. The method of claim 1 wherein, in step (c), the intermediate of formula II is reacted with trimethyl or triethyl borate.

3. The method of claim 1, wherein the linking group X is a saturated 2- to 3-membered hydrocarbon chain; a saturated 2- to 3-membered hydrocarbon chain which constitutes part of a C₅₋₁₂ carbocyclic system which may optionally contain unsaturations or ring fusions; a 2- to 3-membered hydrocarbon chain which constitutes part of an aromatic ring system; or, X is a group of the formula $-(CH_2)_n-NH-(CH_2)_m-$, wherein n and m are each 2 or 3; wherein such groups may be unsubstituted or substituted by one or more C₁₋₃alkyl or phenyl groups.
4. The method of claim 1 wherein the esterification in step (e) is carried out with a diol selected from the group consisting of ethylene glycol, pinacol, catechol, pinanediol, butan-2,3-diol, diethanolamine, and 1,2-diphenylethan-1,2-diol.
5. The method of claim 4 wherein the diol is optically active pinanediol.
6. The method of claim 5, wherein the N-protected pinanediol ester formed in step (e) of claim 1 is further separated into its diastereoisomers.
7. The method of claim 5, wherein the N-deprotected pinanediol ester formed in step (f) of claim 1 is further separated into its diastereoisomers.

8. The method of claim 1, wherein R is tert-butyl, benzyl, trimethylsilylethyl, phenyl, methyl, or ethyl.

9. A method for making a prolineboronic acid ester of the formula VII

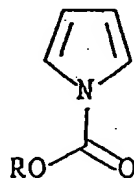


(VII)

wherein X is a linking group,

which method comprises:

- a) treating pyrrole with an activated derivative of carbonic acid, to yield an N-protected pyrrole of the formula I



(I)

wherein R is C₁₋₆alkyl, C₃₋₆cycloalkyl, benzyl, phenyl, phenyl substituted with one or more C₁₋₆alkyl groups, or trimethylsilylethyl,

b) treating the protected intermediate of the formula I with a lithiating agent, to yield an intermediate of the formula II



wherein R is as defined above,

c) reacting the intermediate of formula II with a trialkyl borate, wherein each alkyl group may be straight, branched or cyclic and contains 1 to 6 carbon atoms, followed by acid catalyzed hydrolysis, to yield an intermediate of the formula III



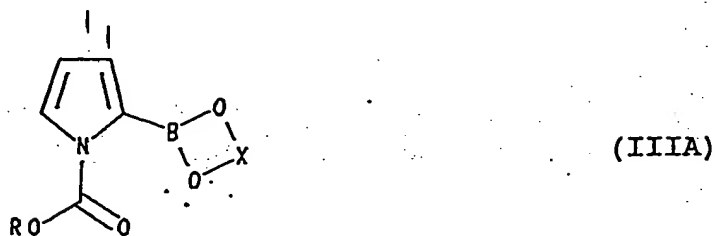
wherein R is as defined above,

d) reacting the compound of formula III with a diol of the formula V,



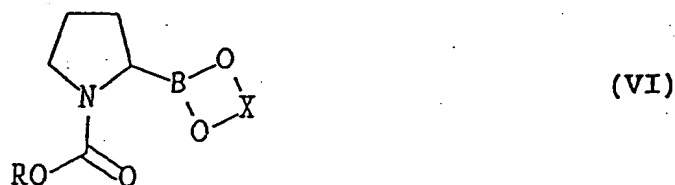
wherein X is a linking group,

to yield a boronate ester of the formula IIIA



wherein R is as defined above,

e) reducing the resulting ester, using catalytic hydrogenation, to yield the proline intermediate of formula VI



and

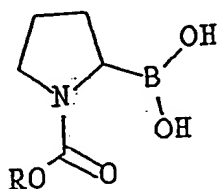
f) removing the protecting group from the nitrogen atom in the proline ring.

10. The method of claim 9 wherein, in step (c), the intermediate of formula II is reacted with trimethyl or triethyl borate.

11. The method of claim 9, wherein the linking group X is a saturated 2- to 3-membered hydrocarbon chain; a saturated 2- to 3-membered hydrocarbon chain which constitutes part of a C₅₋₁₂ carbocyclic system which may optionally contain unsaturations or ring fusions; a 2- to 3-membered hydrocarbon chain which constitutes part of an aromatic ring system; or, X is a group of the formula $-(CH_2)_n-NH-(CH_2)_m-$, wherein n and m are each 2 or 3; wherein such groups may be unsubstituted or substituted by one or more C₁₋₃ alkyl or phenyl groups.
12. The method of claim 9 wherein the esterification in step (d) is carried out with a diol selected from the group consisting of ethylene glycol, pinacol, catechol, pinanediol, butan-2,3-diol, diethanolamine, and 1,2-diphenylethan-1,2-diol.
13. The method of claim 12 wherein the diol is optically active pinanediol.
14. The method of claim 13, wherein the N-protected pinanediol ester formed in step (e) of claim 9 is further separated into its diastereoisomers.
15. The method of claim 13, wherein the N-deprotected pinanediol ester formed in step (f) of claim 9 is further separated into its diastereoisomers.

16. The method of claim 9, wherein R is tert-butyl, benzyl, trimethylsilylethyl, phenyl, methyl, or ethyl.

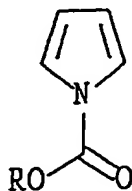
17. A method for making an intermediate of the formula IV



(IV)

which method comprises:

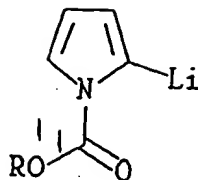
- a) treating pyrrole with an activated derivative of carbonic acid, to yield an N-protected pyrrole of the formula I



(I)

wherein R is C₁₋₆alkyl, C₃₋₆cycloalkyl, benzyl, phenyl, phenyl substituted with one or more C₁₋₆alkyl groups, or trimethylsilylethyl,

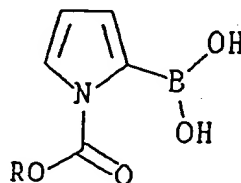
- b) treating the protected intermediate of the formula I with a lithiating agent, to yield an intermediate of the formula II



(II)

wherein R is as defined above,

c) reacting the intermediate of formula II with a trialkyl borate, wherein each alkyl group may be straight, branched or cyclic and contains 1 to 6 carbon atoms, followed by acid catalyzed hydrolysis, to yield an intermediate of the formula III

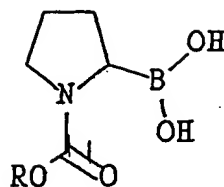


(III)

wherein R is as defined above, and,

d) reducing the compound of formula III, using catalytic hydrogenation, in order to yield the proline intermediate of formula IV.

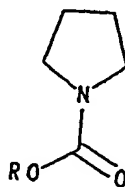
18. A method for making an intermediate of the formula IV



(IV)

which method comprises:

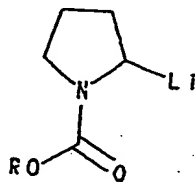
- a) treating pyrrolidine with an acylating agent, to yield a protected pyrrolidine of the formula VIII



(VIII)

wherein R is C₁₋₆alkyl, C₃₋₆cycloalkyl, benzyl, phenyl, phenyl substituted with one or more C₁₋₆alkyl groups, or trimethylsilylethyl,

- b) treating the compound of formula VIII with a lithiating agent, to yield a compound of the formula IX



(IX)

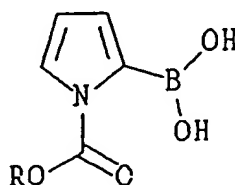
wherein R is as defined before,

c) reacting the compound of formula IX with a trialkyl borate, wherein each alkyl group may be straight, branched or cyclic and may contain 1 to 6 carbon atoms, and

d) hydrolyzing the product of the previous step, to yield the compound of formula IV.

19. The method of claim 18 wherein, in step (c), the intermediate of formula IX is reacted with trimethyl or triethyl borate.

20. An intermediate of the formula III



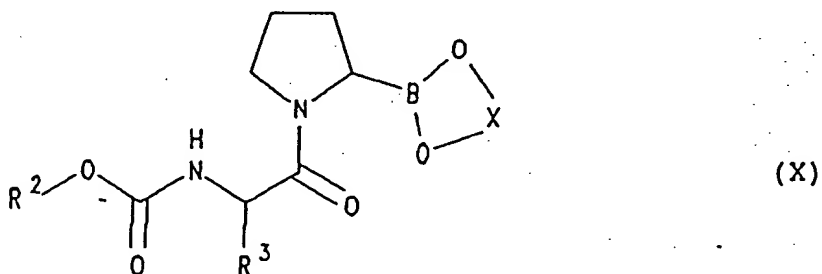
(III)

wherein R is C₁₋₆alkyl, C₃₋₆cycloalkyl, benzyl, phenyl, phenyl substituted with one or more C₁₋₆alkyl groups, or trimethylsilylethyl.

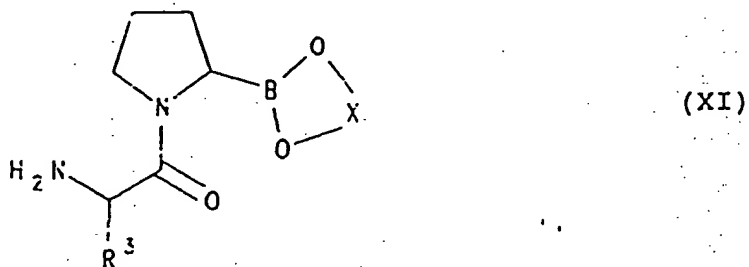
21. 1-(1,1-Dimethylethoxycarbonyl)-pyrrole-2-boronic acid.

22. A compound selected from the group consisting of
(1S,2S,3R,5S)-pinanediol
1-(1,1-dimethylethoxycarbonyl)-pyrrolidine-2S-
boronate;
(1S,2S,3R,5S)-pinanediol
1-(1,1-dimethylethoxycarbonyl)-pyrrolidine-2R-
boronate;
(1R,2R,3S,5R)-pinanediol
1-(1,1-dimethylethoxycarbonyl)-pyrrolidine-2S-
boronate; and (1R,2R,3S,5R)-pinanediol
1-(1,1-dimethylethoxycarbonyl)-pyrrolidine-2R-
boronate.
23. A compound selected from the group consisting of
(1S,2S,3R,5S)-pinanediol pyrrolidine-2S-boronate
hydrochloride; (1S,2S,3R,5S)-pinanediol
pyrrolidine-2R-boronate hydrochloride;
(1R,2R,3S,5R)-pinanediol pyrrolidine-2S-boronate
hydrochloride; (1R,2R,3S,5R)-pinanediol
pyrrolidine-2R-boronate hydrochloride.
24. A compound selected from the group consisting of
(1S,2S,3R,5S)-pinanediol
1-(1,1-dimethylethoxycarbonyl)-pyrrole-2-boronate;
and (1R,2R,3S,5R)-pinanediol
1-(1,1-dimethylethoxycarbonyl)-pyrrole-2-boronate.

25. A method for removing pinanediol as the protective ester group from a boronate ester which method comprises treating such a boronate ester with an oxidizing agent which is capable of cleaving 1,2-diols.
26. The method of claim 25, wherein said oxidizing agent is sodium metaperiodate.
27. A method for removing pinanediol as the protective ester group from a compound of the formula X

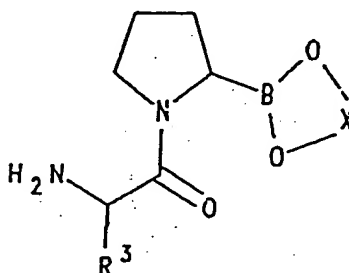


wherein R^2 is a protecting group, and R^3 is the side chain of a naturally occurring amino acid, optionally with appropriate protecting groups, or from a compound of the formula XI



wherein R^3 is as defined above, which method comprises treating such a boronate ester with an oxidizing agent which is capable of cleaving 1,2-diols.

28. The method of claim 27, wherein said oxidizing agent is sodium metaperiodate.
29. A method for removing pinanediol as the protective ester group from a boronate ester having a free amine group, which method comprises applying an aqueous solution of such boronate ester to a column of a cation exchange resin, eluting the column with water or dilute aqueous acid to remove the pinanediol, and finally eluting the column with dilute aqueous base to remove the free boronic acid product.
30. The method of claim 29, wherein said column material is a strongly acidic cation exchange resin.
31. A method for removing pinanediol as the protective ester group from a compound of the formula XI

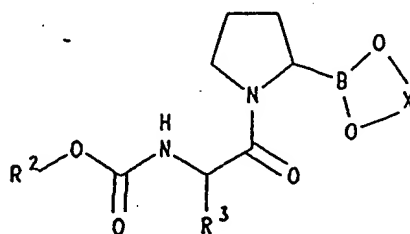


(XI)

wherein R^3 is the side chain of a naturally occurring amino acid, optionally with appropriate protecting groups, which method comprises applying an aqueous solution of such a boronate ester to a column of a cation exchange resin, eluting the column with water or dilute aqueous acid to remove the pinanediol, and finally eluting the column with dilute aqueous base to remove the free boronic acid product.

32. The method of claim 31, wherein said column material is a strongly acidic cation exchange resin.

33. An intermediate of the formula X

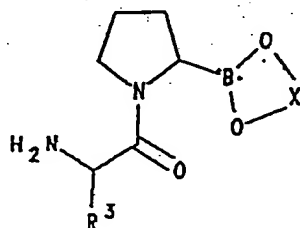


(X)

wherein the protecting group $-O-X-O-$ is derived from pinanediol, and wherein R^2 is a protecting group, and R^3 is the side chain of a naturally occurring amino acid, optionally with appropriate protecting groups.

34. N-(1,1-Dimethylethoxycarbonyl)-L-valylpyrrolidine-2R-boronate (1S,2S,3R,5S)-pinanediol ester.

35. An intermediate of the formula XI

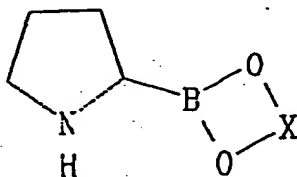


(XI)

wherein the protecting group -O-X-O- is derived from pinanediol, and wherein R³ is the side chain of a naturally occurring amino acid, optionally with appropriate protecting groups.

36. L-Valylpyrrolidine-2R-boronate (1S,2S,3R,5S)-pinanediol ester or a salt thereof.

37. A method for making a prolineboronic acid ester of the formula VII

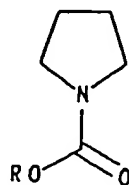


(VII)

wherein X is a linking group,

which method comprises:

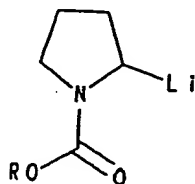
- a) treating pyrrolidine with an acylating agent, to yield a protected pyrrolidine of the formula VIII



(VIII)

wherein R is C₁₋₆alkyl, C₃₋₆cycloalkyl, benzyl, phenyl, phenyl substituted with one or more C₁₋₆alkyl groups, or trimethylsilylethyl,

- b) treating the compound of formula VIII with a lithiating agent, to yield a compound of the formula IX

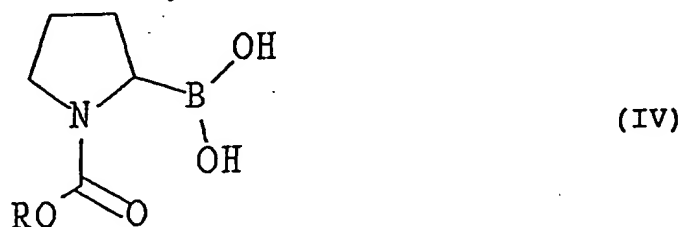


(IX)

wherein R is as defined before,

c) reacting the compound of formula IX with a trialkyl borate, wherein each alkyl group may be straight, branched or cyclic and may contain 1 to 6 carbon atoms, and

d) hydrolyzing the product of the previous step, to yield a compound of the formula IV

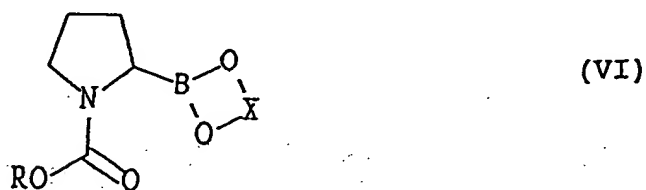


e) reacting the compound of formula IV with a diol of the formula V,



wherein X is the same linking group mentioned above,

to yield a boronate ester of the formula VI

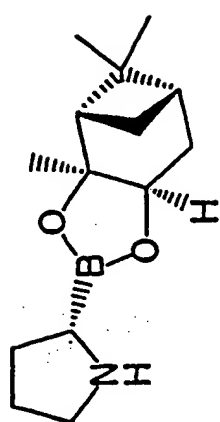


wherein X is the same linking group mentioned above and R is as defined above, and

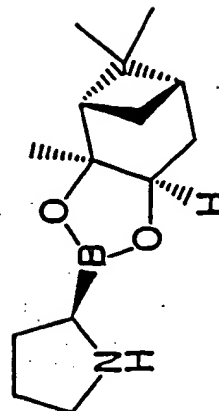
f) removing the protecting group from the nitrogen atom in the proline ring.

38. The method of claim 37 wherein, in step (c), the intermediate of formula IX is reacted with trimethyl or triethyl borate.
39. The method of claim 37, wherein the linking group X is a saturated 2- to 3-membered hydrocarbon chain; a saturated 2- to 3-membered hydrocarbon chain which constitutes part of a C₅₋₁₂ carbocyclic system which may optionally contain unsaturations or ring fusions; a 2- to 3-membered hydrocarbon chain which constitutes part of an aromatic ring system; or, X is a group of the formula $-(CH_2)_n-NH-(CH_2)_m-$, wherein n and m are each 2 or 3; wherein such groups may be unsubstituted or substituted by one or more C₁₋₃ alkyl or phenyl groups.
40. The method of claim 37 wherein the esterification in step (e) is carried out with a diol selected from the group consisting of ethylene glycol, pinacol, catechol, pinanediol, butan-2,3-diol, diethanolamine, and 1,2-diphenylethan-1,2-diol.

41. The method of claim 40 wherein the diol is optically active pinanediol.
42. The method of claim 41, wherein the N-protected pinanediol ester formed in step (e) of claim 37 is further separated into its diastereoisomers.
43. The method of claim 41, wherein the N-deprotected pinanediol ester formed in step (f) of claim 37 is further separated into its diastereoisomers.
44. The method of claim 37, wherein R is tert-butyl, benzyl, trimethylsilylethyl, phenyl, methyl, or ethyl.



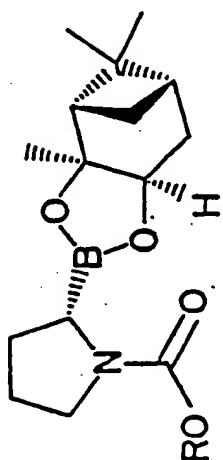
VIIa



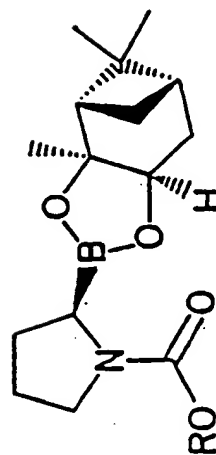
VIIb

HCl
EtOAc

HCl
EtOAc



VIa



VIb

IV

Fig- 1

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 92/09845

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07F5/02		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07F	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	WO,A,9 116 339 (NEW ENGLAND MEDICAL CENTER HOSPITALS, INC.) 31 October 1991 ---	20-24, 33-36
A	WO,A,8 903 223 (BACHOVCHIN, W.W. ET AL.) 20 April 1989 see the whole document ---	20-24, 33-36
P,X	EP,A,0 471 651 (SANDOZ LTD.) 19 February 1992 see the whole document -----	1-44
<p>* Special categories of cited documents :¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
18 FEBRUARY 1993		12.03.93
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		RINKEL L.J.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9209845
SA 67275

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 18/02/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9116339	31-10-91	None	
WO-A-8903223	20-04-89	US-A- 4935493 AU-A- 2801289	19-06-90 02-05-89
EP-A-0471651	19-02-92	AU-A- 8179291 CA-A- 2048953 JP-A- 4330094	20-02-92 14-02-92 18-11-92